The advantage of the likelihood-based approach used in other studies is that it incorporates the phenotypes of all subjects, irrespective of whether their genotypes are known, properly allowing for uncertainty about the genotypes of untyped subjects (*1*). Perhaps the cancer and genotyping data on all 104 families, including individuals for whom DNA was not available, could be presented in a format that permits independent analysis [see, e.g., Table 1 from (*5*)].

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THE NEW YORK BREAST CANCER STUDY (NYBCS) Group Report ("Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*," M.-C. King *et al.*, 24 Oct. 2003, p. 643) states that their results "indicate that breast and ovarian cancer risks among *BRCA1* or *BRCA2* mutation carriers who are ascertained through a single affected relative are as high as risks observed in multiply affected families." We disagree. The design, implementation, and analysis of the NYBCS could have led to serious overestimation of penetrance because of ascertainment bias. Their attempts to rule out overestimation are not convincing. Family members must be enrolled irrespective of disease status to achieve unbiased penetrance estimates. That is, a carrier relative who dies from heart disease and one who dies from breast cancer must be equally available for genotyping and subsequent inclusion in the analysis.

1) When only confirmed carriers are included, availability of tumor blocks as a source of DNA for genotyping could influence who is included.

2) Relatives with breast or ovarian cancer, particularly distant relatives, might be more likely to be reported by probands and enrolled by investigators.

3) The authors excluded the entire sibship when one female sibship member could not be genotyped directly or by reconstruction. This strategy could increase net bias because one refuser can exclude the entire sibship; this may be more likely to occur when there are no affected women in the sibship and in older sibships. Also, this strategy gives no protection from bias in a one-female sibship. Presentation of numbers of relatives according to relationship to proband, cancer status, and method of determining carrier status (blood, blocks, or inferred) would help the reader evaluate the importance of ascertainment bias.

4) A study based on relatives of cancer patients is not optimal for assessing heterogeneity of risk for carriers in different families (*1*–*5*) because relatives in higher-risk families, if any, will be overrepresented. In the extreme, women in families segregating a mutation but having no breast cancer in the pedigree are excluded from all analyses because only breast cancer cases can be probands. Moreover, if carrier relatives from the 52 low-incidence families constitute half of all carrier women, the difference between penetrance in high-incidence and low-incidence families would be double the difference between entries in tables S2C and S2A; for example, at age 70, the difference would be 18 percentage points (62% versus 80%).

5) Probands were ascertained from 12 "major cancer centers" and affiliated private practitioners. Patients from "low-incidence" families may be more likely to be treated at community hospitals and be missed by this study. Similarity of mutation prevalence at each cancer center does not address this concern.

6) Probands were Jewish breast cancer patients referred to the study team by clinicians. Women of uncertain ethnicity but with a strong family history may have been referred more often than women with no family history. Although the NYBCS provides data comparing family history of refusers and participants, they cannot investigate family history of carriers not referred by participating physicians, and the pool of individuals from which referred cases were drawn is not known.

Penetrance estimates from truly population-based designs (*2*, *4*, *6*) and a large survey of a Jewish community (*1*, *3*) are lower than those from multiplex consortium families (*7*) and the NYBCS. If families segregating *BRCA* mutations have wide variation in risk, differences in penetrance estimates among studies may reflect differences in the proportion of carriers enrolled from higher or lower risk families (*1*, *2*, *4*, *5*). Because the NYBCS does not show convincingly that carriers with no or modest family history have nearly the same penetrance as carriers with extensive family history, it does not provide new support for recommendations of broader screening given in the accompanying Perspective ("A risky business—assessing breast cancer risk," E. Levy-Lahad, S. E. Plon, 24 Oct. 2003, p. 574).

We agree that environmental and genetic factors can lead to heterogeneity of risk among individual carriers (*8*, *9*). However, the design and analysis of the New York study do not reliably investigate them. With additional consideration of the methodologic issues raised here, results about penetrance and cofactors from the NYBCS can be better integrated with the extensive body of published evidence.

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Response

RESULTS OF THE NEW YORK BREAST CANCER Study (NYBCS) (*1*) were that lifetime risks of breast cancer associated with inherited mutations in *BRCA1* and *BRCA2* in the present-day American Ashkenazi Jewish population exceed 80%, that these risks apply to mutation carriers regardless of their family history of breast or ovarian cancer, and that breast cancer risks to mutation carriers have changed over time due to influences of nongenetic factors. The premise of the Letters of Easton *et al*. and Wacholder *et al*. is that NYBCS estimates of breast cancer risk among carriers of *BRCA1* and *BRCA2* mutations are substantially higher at all ages than are penetrance estimates from previous analyses. The Letters' authors then suggest various biases to which they believe the NYBCS could have been subject, leading to these putatively high penetrance estimates.

We disagree with this premise. The first table (p. 1289) compares penetrance estimates for carriers of mutations in *BRCA1* or *BRCA2* from several studies (*1*–*5*). These studies, from four groups, are those most frequently cited in the literature, involve most of the authors of the two critiques, are the largest collections of original data on this topic, and represent four different study designs [see Supporting Online Material (SOM) for more details] (*6*).

As indicated in the first table, estimates of breast cancer risk for mutation carriers for ages up to 60 years are similar in all the studies. Such close concordance is striking,